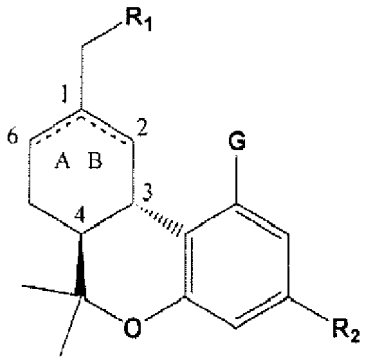
Amendments to the Claims

The following listing of claims replaces all prior listings and version of claims in this application.

1. (Previously Presented) A compound of the general Formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A-----B indicates an optional 1(2) or 6(1) double bond,

R_1 is

A) R_3 where R_3 is selected from the group consisting of

a) a linear or branched, saturated or unsaturated, carbon side chain comprising 1-8 carbon atoms and 1-3 heteroatoms, at least one heteroatom being placed between two carbon atoms; or

b) a saturated or unsaturated cyclic moiety or an aromatic or heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms,

said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from

i) C_{1-6} alkyl,

ii) C_{1-6} alkoxy,

iii) C_{1-6} alkylthio,

iv) halo,

v) carboxyl,

vi) $-CO_2-C_{1-4}$ alkyl,

vii) keto,

viii) nitro, and

ix) a saturated or unsaturated cyclic moiety, or an aromatic or a heterocyclic moiety having from 5-20 atoms comprising one or two ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S;

wherein each ring optionally is further substituted with one or more groups selected from i)-viii) as defined above;

B) an amine or an amide substituted with at least one substituent as defined in R_3 above;

C) a thiol, a sulfide, a sulfoxide, a sulfone, a thioester or a thioamide optionally substituted with one substituent as defined in R_3 above; or

D) an ether $-OR_3$ wherein R_3 is as defined above;

G is (a) halogen, (b) C_1-C_6 alkyl, or (c) -OR wherein R is (a') -R'', wherein R'' is hydrogen or C_1-C_6 alkyl optionally containing a terminal -OR''' or -OC(O)R''' moiety wherein R''' is hydrogen or C_1-C_6 alkyl, or (b') -C(O)R''' wherein R''' is as previously defined, and

$\mathbf{R_2}$ is (a) C_1-C_{12} alkyl, (b) -OR'''', in which R'''' is a straight chain or branched C_2-C_9 alkyl which may be substituted at the terminal carbon atom by a phenyl group, or (c) $-(CH_2)_nOR'''$ wherein n is an integer of 1 to 7 and R''' is hydrogen or C_1-C_6 alkyl;

with the proviso that $\mathbf{R_1}$ is other than a heterocyclic moiety having a labile hydrogen atom so that said moiety acts as a carboxylic acid analogue.

2. (Previously Presented) The compound according to claim 1 wherein $\mathbf{R_1}$ is a saturated or unsaturated cyclic moiety, an aromatic moiety or a heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; optionally further substituted with at least one substituent selected from the group consisting of lower alkyl, halogen, nitro, cyano, -SR''', -NHR''', $-N(R''')_2$,

-OR''', -COR''', -C(O)OR''' or NH-COR''' moiety wherein R''' is hydrogen or C_1-C_6 alkyl.

3. (Original) The compound according to claim 1 wherein $\mathbf{R_1}$ is a heterocyclic moiety selected from the group consisting of an imidazolyl, an imidazolinyl, a morpholino, a piperidyl, a piperazinyl, a pyrazolyl, a pyrrolyl, a pyrrolidinyl, a triazolyl, and a tetrazolyl, optionally further substituted wherein the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, keto, carboxy, or nitro, wherein C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

4. (Original) The compound according to claim 1 wherein $\mathbf{R_1}$ is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazolinyl, or 4-methylpiperidinyl.

5. (Original) The compound according to claim 1 wherein A-----B is a 6(1) double bond and **G** is –OH or lower acyloxy.

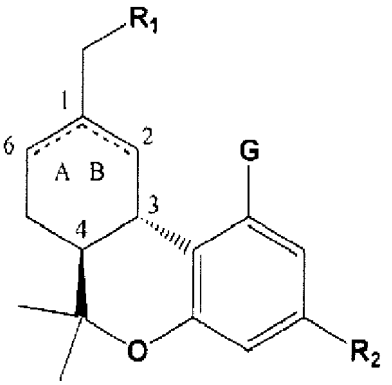
6. (Original) The compound according to claim 5 wherein $\mathbf{R_2}$ is 1,1-dimethylheptyl or 1,2-dimethylheptyl and wherein $\mathbf{R_1}$ is selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, tetrahydropyridine, pyrazoline, oxazoline, pyrrolidine, imidazoline, 2-thio-imidazole, 2-methylthio-imidazoline, 4-methyl-2-imidazoline, 4,4-dimethyl-2-imidazoline, methyl sulfide, methylsulfoxide, acetamido, benzamide, cyano, 1,2,4-triazole, 1,3,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, thiophene, phenyl, morpholine, thiomorpholine, thiazolidine, glycerol, piperazine, piperidine and tetrahydropyran, optionally further substituted wherein the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, keto, carboxy , or nitro, wherein C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

7. (Original) The compound according to claim 6 wherein $\mathbf{R_1}$ is imidazole, pyrazole, 2-methyl thio-2-imidazoline, or 4-methylpiperidine.

8. (Original) The compound according to claim 1 wherein A-----B is absent and **G** is -OH or lower acyloxy.

9. (Previously Presented) The compounds according to claim 1 selected from the group consisting of: (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(imidazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1 -hydroxy-9-(pyrazolomethyl)-6a,7,10,l0a- tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(1H-imidazol-2-ylsulfanyl methyl)-6a,7,10,10a- tetrahydro-6H- dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-piperidinopiperidine methyl)-6a,7,10,10a- tetrahydro-6H-dibenzo[b,d]pyran; and (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-methylpiperidine methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran.

10. (Previously Presented) A pharmaceutical composition comprising as an active ingredient a compound of the general formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A-----B indicates an optional 1(2) or 6(1) double bond,

R_1 is

A) R_3 where R_3 is selected from the group consisting of

a) a linear or branched, saturated or unsaturated, carbon side chain comprising 1-8 carbon atoms and 1-3 heteroatoms, at least one heteroatom being placed between two carbon atoms; or

b) a saturated or unsaturated cyclic moiety or an aromatic or heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms,

said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from

i) C_{1-6} alkyl,

ii) C_{1-6} alkoxy,

iii) C_{1-6} alkylthio,

iv) halo,

v) carboxyl,

vi) $-CO_2-C_{1-4}$ alkyl,

vii) keto,

viii) nitro, and

ix) a saturated or unsaturated cyclic moiety, or an aromatic or a heterocyclic moiety comprising one or two ringed structures wherein each ring comprises 3-8 carbons ~~interrupted by~~ and 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S;

wherein each ring optionally is further substituted with one or more groups selected from i)-viii) as defined above;

B) an amine or an amide substituted with at least one substituent as defined in R_3 above;

C) a thiol, a sulfide, a sulfoxide, a sulfone, a thioester or a thioamide optionally substituted with one substituent as defined in R_3 above; or

D) an ether $-OR_3$ wherein R_3 is as defined above;

G is (a) halogen, (b) C_1-C_6 alkyl, or (c) -OR wherein R is (a') -R'', wherein R'' is hydrogen or C_1-C_6 alkyl optionally containing a terminal -OR''' or -OC(O)R''' moiety wherein R''' is hydrogen or C_1-C_6 alkyl, or (b') -C(O)R''' wherein R''' is as previously defined, and

$\mathbf{R_2}$ is (a) C_1-C_{12} alkyl, (b) -OR"", in which R"" is a straight chain or branched C_2-C_9 alkyl which may be substituted at the terminal carbon atom by a phenyl group, or (c) $-(CH_2)_nOR'''$ wherein n is an integer of 1 to 7 and R''' is hydrogen or C_1-C_6 alkyl;
with the proviso that $\mathbf{R_1}$ is other than a heterocyclic moiety having a labile hydrogen atom so that said moiety acts as a carboxylic acid analogue;
together with a pharmaceutically acceptable diluent or carrier.

11. (Previously Presented) The composition according to claim 10 wherein $\mathbf{R_1}$ is a saturated or unsaturated cyclic moiety, an aromatic moiety or a heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; optionally further substituted with at least one substituent selected from the group consisting of lower alkyl, halogen, nitro, cyano, -SR''', -NHR''', $-N(R''')_2$, -OR''', -COR''' , -C(O)OR''' or NH-COR''' moiety wherein R''' is hydrogen or C_1-C_6 alkyl.

12. (Original) The composition according to claim 10 wherein $\mathbf{R_1}$ is a heterocyclic moiety selected from the group consisting of an imidazolyl, an imidazolinyl, a morpholino, a piperidyl, a piperazinyl, a pyrazolyl, a pyrrolyl, a pyrrolidinyl, a triazolyl, and a tetrazolyl, optionally further substituted wherein the substituent is selected from the group consisting of $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyloxy, $C_{1\text{-}6}$ alkylthio, keto, carboxy, or nitro, wherein $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy and $C_{1\text{-}6}$ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

13. (Original) The composition according to claim 10 wherein $\mathbf{R_1}$ is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazolinyl, or 4-methylpiperidinyl.

14. (Original) The composition according to claim 10, wherein A-----B is a 6(1) double bond, and **G** is -OH or lower acyloxy.

15. (Original) The composition according to claim 14 wherein $\mathbf{R_2}$ is 1,1-dimethylheptyl or 1,2-dimethylheptyl and wherein $\mathbf{R_1}$ is selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, tetrahydropyridine, pyrazoline, oxazoline, pyrrolidine, imidazoline, 2-thio-imidazole, 2-methylthio-imidazoline, 4-methyl-2-imidazoline, 4,4-dimethyl-2-imidazoline, methyl sulfide, methylsulfoxide, acetamido, benzamide, cyano, 1,2,4-triazole, 1,3,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, thiophene, phenyl, morpholine, thiomorpholine, thiazolidine, glycerol, piperazine, piperidine and tetrahydropyran, optionally further substituted wherein the substituent is selected from the group consisting of $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyloxy, $C_{1\text{-}6}$ alkylthio, keto, carboxy, or nitro, wherein $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy and $C_{1\text{-}6}$ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

16. (Original) The composition according to claim 15 wherein $\mathbf{R_1}$ is imidazole, pyrazole, 2-methyl thio-2-imidazoline, or 4-methylpiperidine.

17. (Original) The composition according to claim 10 wherein A-----B is absent and G is OH or a lower acyloxy group.

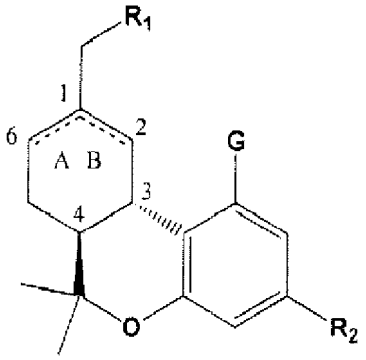
18. (Previously Presented) The composition according to claim 10 wherein the active ingredient is selected from the group consisting of: (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(imidazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(pyrazolomethyl)-6a,7,10,l0a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(1H-imidazol-2-ylsulfanyl methyl)-6a,7,10,10a-tetrahydro-6H- dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-piperidinopiperidinemethyl)-6a,7,10,10a- tetrahydro-6H-dibenzo[b,d]pyran; and (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy -9-(4-methylpiperidine methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran.

19. (Original) The composition according to claim 10 wherein the carrier or diluent is an aqueous cosolvent solution comprising a pharmaceutically acceptable cosolvent,

a micellar solution prepared with natural or synthetic ionic or non-ionic surfactants, or a combination of such cosolvent and micellar solutions.

20. (Original) The composition according to claim 19 wherein the carrier is (a) a solution of ethanol, a surfactant, and water or (b) an emulsion comprising a triglycerides, lecithin, glycerol, an emulsifier, an antioxidant, and water.

21. (Currently Amended) A method for treating ~~or alleviating~~ inflammation caused by edema or inducing prostaglandin synthesis; neural injury caused by edema, ischemia, head trauma, stroke, or spinal cord injury; Parkinson's Disease; optic neuropathy; ischemic damage to the cardiovascular system; pain; ~~inflammatory diseases or disorders, damage resulting from ischemia, injuries to the central nervous system and neurodegenerative disorders, pain, autoimmune diseases, cardiovascular disorders, or~~ drug abuse, tolerance or dependence, or providing axonal regeneration by administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a compound of the formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A-----B indicates an optional 1(2) or 6(1) double bond,

R_1 is

A) R_3 where R_3 is selected from the group consisting of

a) a linear or branched, saturated or unsaturated, carbon side chain comprising 1-8 carbon atoms and 1-3 heteroatoms, at least one heteroatom being placed between two carbon atoms; or

b) a saturated or unsaturated cyclic moiety or an aromatic or heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms,

said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from

i) C_{1-6} alkyl,

ii) C_{1-6} alkoxy,

iii) C_{1-6} alkylthio,

iv) halo,

v) carboxyl,

vi) $-CO_2-C_{1-4}$ alkyl,

vii) keto,

viii) nitro, and

ix) a saturated or unsaturated cyclic moiety, or an aromatic or a heterocyclic moiety comprising one or two ringed structures wherein each ring comprises 3-8 carbons and 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S;

wherein each ring optionally is further substituted with one or more groups selected from i)-viii) as defined above;

B) an amine or an amide substituted with at least one substituent as defined in R_3 above;

C) a thiol, a sulfide, a sulfoxide, a sulfone, a thioester or a thioamide optionally substituted with one substituent as defined in R_3 above; or

D) an ether $-OR_3$ wherein R_3 is as defined above;

G is (a) halogen, (b) C_1-C_6 alkyl, or (c) -OR wherein R is (a') -R'', wherein R'' is hydrogen or C_1-C_6 alkyl optionally containing a terminal -OR''' or -OC(O)R''' moiety wherein R''' is hydrogen or C_1-C_6 alkyl, or (b') -C(O)R''' wherein R''' is as previously defined, and

R_2 is (a) C_1-C_{12} alkyl, (b) -OR'''', in which R'''' is a straight chain or branched C_2-C_9 alkyl which may be substituted at the terminal carbon atom by a phenyl group, or (c) $-(CH_2)_nOR'''$ wherein n is an integer of 1 to 7 and R''' is hydrogen or C_1-C_6 alkyl;

with the proviso that $\mathbf{R_1}$ is other than a heterocyclic moiety having a labile hydrogen atom so that said moiety acts as a carboxylic acid analogue.

22. (Previously Presented) The method according to claim 21 wherein $\mathbf{R_1}$ is a saturated or unsaturated cyclic moiety, an aromatic moiety or a heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons and 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; optionally further substituted with at least one substituent selected from the group consisting of lower alkyl, halogen, nitro, cyano, -SR''', -NHR''', -N(R''')$_2$, -OR''', -COR''', -C(O)OR''' or NH-COR''' moiety wherein R''' is hydrogen or C_1-C_6 alkyl.

23. (Original) The method according to claim 21 wherein $\mathbf{R_1}$ is a heterocyclic moiety selected from the group consisting of an imidazolyl, an imidazolinyl, a morpholino, a piperidyl, a piperazinyl, a pyrazolyl, a pyrrolyl, a pyrrolidinyl, a triazolyl, and a tetrazolyl, optionally further substituted wherein the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, keto, carboxy, or nitro, wherein C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

24. (Original) The method according to claim 21 wherein $\mathbf{R_1}$ is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazolinyl, or 4-methylpiperidinyl.

25. (Original) The method according to claim 21 wherein A-----B is a 6(1) double bond, and G is -OH or lower acyloxy.

26. (Original) The method according to claim 25 wherein $\mathbf{R_2}$ is 1,1-dimethylheptyl or 1,2-dimethylheptyl and wherein $\mathbf{R_1}$ is selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, tetrahydropyridine, pyrazoline, oxazoline, pyrrolidine, imidazoline, 2-thio-imidazole, 2-methylthio-imidazoline, 4-methyl-2-imidazoline, 4,4-dimethyl-2-imidazoline, methyl sulfide, methylsulfoxide, acetamido,

benzamide, cyano, 1,2,4-triazole, 1,3,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, thiophene, phenyl, morpholine, thiomorpholine, thiazolidine, glycerol, piperazine, piperidine and tetrahydropyran, optionally further substituted wherein the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, keto, carboxy, or nitro, wherein C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures

27. (Original) The method according to claim 26 wherein $\mathbf{R_1}$ is imidazole, pyrazole, 2-methyl thio-2-imidazoline, or 4-methylpiperidine.

28. (Original) The method according to claim 21 wherein A-----B is absent and **G** is -OH or lower acyloxy.

29. (Previously Presented) The method according to claim 21 wherein said compound is selected from the group consisting of: (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(imidazolo methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(pyrazolomethyl)-6a,7,10,l0a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(1H-imidazol-2-ylsulfanylmethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy -9-(4-piperidinopiperidinemethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; and (+)-(3S,4S) -6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-methylpiperidine methyl)-6a,7,10,10a-tetrahydro-6H- dibenzo[b,d]pyran.

30. (Original) The method according to claim 21 wherein said compound is administered in a manner to protect against excitatory amino acid-mediated neurotoxicity.

31. (Original) The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with tolerance or dependence to opioids, cocaine, psychostimulants or alcohol.

32. (Cancelled)

33. (Cancelled)

34. (Original) The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with chronic, neuropathic or other pain.

35. (Cancelled)

36. (Cancelled)

37. (Original) The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with ischemic and/or inflammatory damage to body organs including the lungs, liver, kidney or joints related to pulmonary, hepatic, or renal ischemias, rheumatoid arthritis or septic shock.

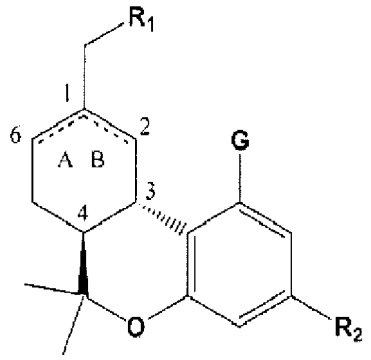
38. (Cancelled)

39. (Original) The method according to claim 21 wherein the daily dosage of said compound is between 0.01 and 25 mg/kg.

40. (Original) The method according to claim 21 wherein the composition is administered orally, parenterally, intravenously, intramuscularly, intralesionally, subcutaneously, transdermally, intratechally, rectally or intranasally.

41. (Currently Amended) A method for treating ~~or alleviating~~ an inflammatory condition caused by edema; ~~excitatory amino acid-mediated neurotoxicity;~~ tolerance to or dependence on opioids~~, cocaine, psychostimulants or alcohol~~; symptoms associated with chronic, neuropathic or other pain; neural injury caused by edema, cerebral ischemia, head trauma, or stroke ~~or spinal cord injury~~; Parkinson's disease; or myocardial infarction by

administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a compound of the formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A-----B is a 6(1) double bond; R_1 is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazolinyl, or 4-methylpiperidinyl; G is –OH or lower acyloxy; and R_2 is C_1-C_{12} alkyl.

42. (Previously Presented) The method according to claim 41, wherein G –OH and R_2 is 1,1-dimethylheptyl.